Remarks

Claims 13-24 are pending and under consideration after the cancellation of claims 1-12 herein. Claims 13, 14, 15 and 22 are amended. Claim 22 is amended to correct the misspelling of "nasopharynx." New claims 25 - 29 are added with support as laid out below. No new matter is believed to be added by the amendments or new claims. Entry and consideration of the amendments and new claims are respectfully requested.

Objection to the Specification

The disclosure is objected to because of the following informalities: page 4, line 4, *"pnueumoniae"* should be *"pneumoniae";* line 10, "pnuemococcal" should be pneumococcal"; and on line 25, the status of U.S. Pat. Appl. 08/222,179 is incorrect. Appropriate correction is provided by the above amendments to the specification.

In this regard these and other obvious misspellings are corrected in amendments to the specification above. The reference to the status of U.S. Patent Application 08/222,179 has been corrected. Thus, withdrawal of these objections is believed to be merited and is respectfully requested.

Rejections Under 35 U.S.C § 112, Second Paragraph

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, because the claim depends from a non-elected claim.

Claim 13 has been amended to make it independent by including the limitations of claim 7. Also, an obvious error in the language of claim 7 has been corrected by reciting that "the first nucleic acid is contiguous with the second nucleic acid" instead of the "the signal sequence of the Borrelia lipoprotein is contiguous with the second nucleic acid sequence." Support for the amendment to claim 13 is found in claim 7 as originally filed. As amended, claim 13 overcomes the rejections and is in condition for allowance.

New claims 25 and 26 have been added. They recite the lipidated PsaA of the invention, but are not in product-by-process format. Support for these claims is found in claims 1 and 2 as filed. These claims are believed to be free of any of the recited rejections, and are believed to be allowable.

Claims 14-19 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is drawn to a protein "having a purity of $\geq$80% and substantially free from contaminant proteins and lipopolysaccharides". The Office Action states that it is unclear what is the relationship of the percent purity and "substantially free" requirement.

In this regard, applicants note that the combination of the percent purity and the "substantially free" requirements means that the recited components are substantially excluded from the < 20% contaminants. Thus, the overall contamination may be up to <20%, but the amount of protein and lipopolysaccharide contamination within the contaminant fraction must be

insubstantial. This meaning is made clear by the use of the word "and" joining the % purity phrase and the "substantially free" phrase.

However, without conceding the point, and only to expedite prosecution, applicants have amended claim 14 to delete reference to percent purity. This is supported in claims 7 and 14 as filed. For the same reasons only, applicants have amended claim 15 to depend from claim 13 as supported in the original dependency to claim 14. Thus, withdrawal of this rejection is believed to be merited and is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions which induce antibodies, allegedly does not reasonably provide enablement for the broad scope of the instant claims, i.e., protective vaccination of animals with any/all preparations of lipidated PsaA. In this regard the Office Action states the following:

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
>
> Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of
> experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.
>
> The nature of the invention - protection of animals against *S. pneumoniae* infection by administration of recombinantly produced, lipidated PsaA.
>
> The state of the prior art provides insufficient guidance for the production of the claimed PsaA or protection administration. Therefore, there is a lack of predictability in the art for the claimed invention.

> The amount of direction or guidance present in the instant specification is insufficient to support the broad scope of the instant claims, e.g., administration of any/all preparations of recombinantly produced lipidated PsaA resulting in protection of recipients against colonization with *S. pneumoniae* following intranasal administration.
>
> The presence only working examples presented in the instant specification for administration of PsaA to animals is Example 3, pages 26-28. In this Example 3, there are four experimental administrations to mice. None of the administrations contain a description of the route of administration of the lipidated PsaA. Therefore, the examiner can not make an accurate assessment for either the presence or lack of support for nasal administration. The first experiment, page 26, line 23 to page 27, line 2, describes adult mice which were given DP2 and the titer of resultant antibodies was measured in the sera. The second experiment, page 27, lines 3-13, utilized two types of recombinant PsA, High Five (H5) and Sf9, given to adult mice. The sera from these mice were tested for antibodies to H5, Sf9, and native PsaA. The third experiment was a passive protection experiment in which infant animals, presumably mice, received sera from adult immunized mice. Following challenge with bacteria, 100% of infant mice receiving Sf9 antisera died at day 10, and 40% of mice receiving H5 sera died.
>
> The fourth and last experiment, page 27, line 21 to page 28, line 6, involved immunization of adult and infant mice with Sf9 or H5 recombinant PsaA. All of the infant mice died following immunization with Sf9. All surviving mice were boosted with immunogen and challenged on day 21. 20% of the infant animals receiving H5 were bacteremic. As stated in the specification "Adult data were inconclusive." Based upon the teachings in the specification one can conclude that: 1) Sf9 by itself kills infant mice, 2) H5 results in 20% of infant animals becoming bacteremic, and 3) neither Sf9 nor H5 produce conclusive protection in adult mice.
>
> Thus, from the incomplete data of the only example in the specification, the quantity of experimentation necessary to fulfill the broad scope of instant claims constitutes merely an invitation to experiment without a reasonable expectation of success.

Regarding factor 2, the state of the art, applicants discount the relevance of the Office's position that insufficient guidance is provided to make the claimed lipidated PsaA. In fact, applicants enable a method that is applicable to the claimed PsaA. This method is recited in claim 7 and is exemplified in the specification with a working example. Thus, the fact that the art may or may not provide such guidance is not germane to the present analysis. The assertion that there is insufficient guidance for protection administration is unsupported. The specification

describes numerous art-recognized and clearly relevant methods of administration, for example "nasal or respiratory administration... dispensed by a squeeze spray dispenser, pump dispenser or aerosol dispenser" (page 22, lines 1 and 2 or PCT publication). Thus, the art provides all the guidance that is needed to perform intranasal administration of a compound.

Regarding factor 3, predictability in the art, lack of predictability asserted in the Office Action is balanced by both 1) the routine nature and quantity of experimentation required to practice the invention and 2) the available data showing protection, which will be discussed in more detail below.

Regarding factor 4, the amount of direction or guidance in the specification, the Office takes the position that the specification is insufficient to support the broad scope of the instant claims, e.g., administration of any/all preparations of recombinantly produced lipidated PsaA resulting in protection of recipients against colonization with *S. pneumoniae* following intranasal administration. As noted above the application teaches how to make the claimed lipidated PsaA, and the Office has not provided any specific basis to challenge the sufficiency of this teaching. The specification also provides extensive description of various art-accepted and relevant methods by which the lipidated PsaA can be formulated and administered (page 19, line 3 – page 22, line 25 of the PCT publication). The guidance includes well-known methods of intranasal administration (see page 22, lines 1 and 2 of PCT publication). The Office has not specifically acknowledged this teaching, and, thus, has not provided any basis for challenging its sufficiency. Also, this is not germane to claim 20, which does not recite intranasal administration. The specification demonstrates examples of protective administration (described in detail below).

Thus, it is very difficult to determine what facts the Office is considering to support its conclusion regarding lack of guidance for the claimed methods.

Regarding factor 5, working examples, the Office Action recites, but appears to disregard significant data showing a protective effect of the lipidated PsaA.

Applicants agree that the first and second examples of *in vivo* administration showed that lipidated PsaA is immunogenic and that antibodies raised in response to immunization with H5-produced lipidated PsaA cross reacted with native and appropriate recombinant PsaA. These experiments establish that lipidated PsaA is an immunogen and that H5-produced lipidated PsaA raises specifically binding antibodies.

Applicants agree that the third example of *in vivo* studies shows effective passive immunization of 60 % of mice receiving sera raised against H5-produced lipidate PsaA. This is a statistically significant example of protection. The fact that not all mice were protected or that lipidated PsaA produced in Sf9 cells was not effective (or was injurious) does not negate the evidence of efficacy. What it does is guide the skilled person to prefer H5 cell-produced lipidated PsaA over Sf9 cell-produced lipidated PsaA for raising antibodies for passive immunization. This is valid animal model data showing the efficacy of a recombinantly expressed lipidated PsaA to produce serum that can passive immunize, i.e., that the lipidated PsaA produces protective antibodies. As such, it must be taken as evidence of the satisfaction of the working examples factor. The Office has stated no basis for requiring more evidence of efficacy than is provided.

Applicants acknowledge that the data in the forth example of *in vivo* administration show that immunization with H5 results in protection of 80% of infant animals. This is a statistically significant showing of efficacy. As such, it must be taken as evidence of the satisfaction of the working examples factor. The Office has stated no basis for requiring more evidence of efficacy than is provided.

Nevertheless, applicants are aware of data showing the enhanced anti-S. pneumoniae effect of lipidated PsaA epitopes compared to non-lipidated epitopes. The epitopes were identified using phage display screening by native PsaA-specific antibodies, and, thus, are indicative of the activity of the native PsaA. Johnson et al. (attached as exhibit A) measured nasopharyngeal carriage of S. pneumoniae before and after immunization with lipidated PsaA epitopes and non-lipidated PsaA epitopes. They found reduction in S. pneumoniae using both the lipidated and non-lipidated epitopes, with the lipidated epitopes having a greater effect. These data demonstrate that lipidated PsaA reduces the amount of bacteria in the context of a recognized infection model.

Regarding factor 6, the quantity of experimentation, the office does not specifically address this factor in the context of the present case. The methods of administration described in the specification are relevant and well-known in the art. Thus, there is no concern that much experimentation would need to be done to accomplish the steps of the immunization/protection method. Regarding the issue of obtaining protection, valid animal model data are already presented to establish this. Thus, the quantity of experimentation needed to practice the invention is relatively small, given the work that has already been done.

Regarding factor 7, the relative skill of one in the art, the office also does not specifically address this factor. In fact, those skilled in the art of immunochemistry/immunology are highly skilled, understand the nature and quantity of work involved to practice a vaccine. Given the substantial amount of guidance and working examples of the claimed methods, it seems unlikely that one of skill in this art would find the process of obtaining proof of efficacy in humans requires undue experimentation. Since this is the only step not explicitly taught herein, the claims should be enabled. This is particularly true when, as in the present case, the claims are not broad, but are focused on a specifically described antigen lipidated as specifically described.

New claims 27-29 are dependent claims that recite wherein the lipidated PsaA is recombinantly produced in a high five cell. Support for these claims is found in the specification at page 27, lines 3-4, 9-11 and 19-20, and page 28, lines 4-6 (PCT publication). These claims capture a specific example of the present immunization compositions and methods that have been demonstrated to provide protection.

In summary, applicants have applied the Forman factors to the actual facts of the present case to demonstrate the enabling disclosure of the application for the claims presently presented. The picture painted is one of routine experimentation only being required to transition from the present teaching to the actual practice of the claimed invention. Thus, withdrawal of this rejection and allowance of claims 20-24 and 27-29 is respectfully requested.

In view of the above amendments and remarks, reconsideration and allowance of the present application are merited and respectfully requested. The Examiner is invited to directly

contact the undersigned to discuss any issues relating to the present application.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $980.00, representing $980.00 for the fee for a large entity under 37 C.F.R. § 1.17(a)(3) is enclosed. No fee is believed due for any of the new claims as at least a corresponding number of claims are canceled herein. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Gwendolyn D. Spratt — Date: 10-13-04